REMARKS

Applicants have reviewed the rejection of claims 12, 31, 45-69 and 71-102 as set out in the instant Final Office Action. After careful consideration, Applicants respectfully traverse this rejection.

Claim Rejection Based on 35 U.S.C. § 112, first paragraph

Claims 12, 31, 45-69 and 71-102 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner asserts that "the claimed invention encompasses ***any gene product*** in a cell whose activity is reduced by ***an antisense***, thereby producing a sensitized cell." Additionally, the Examiner notes, that because of polar effects in bacteria, antisense inhibition of a single known essential gene in an operon might result in the inhibition of expression of other downstream genes present in the operon. The Examiner then asserts that the number of genes and gene products disclosed in the specification does not adequately support the elected claims. In particular, it is alleged that the specification does not provide sufficient species to permit a skilled artisan to envision the structure of the antisense nucleic acids which may be used to carry out the claimed method because the structure of such antisense nucleic acids is highly variant.

Applicants respectfully disagree with the Examiner's construction of the elected claims. The elected claim set comprises two independent claims (claim 12 and 31) as well as claims dependent thereon. Neither of the independent claims (nor the claims dependent thereon) are drawn to an invention that encompasses "***any gene product*** in a cell whose activity is reduced by ***an antisense***, thereby producing a sensitized cell." Rather the claims are drawn to providing an antisense nucleic acid to reduce the activity or amount of a gene product whose activity or amount is reduced by an antisense comprising a nucleotide sequence having a specific sequence identification number. For example, Claim 12, which is drawn to a method for screening a candidate compound for the ability to reduce cellular proliferation, includes, in relevant part, the step of providing a sublethal level of an antisense nucleic acid complementary to at least a portion of a nucleic acid encoding a gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell, ***wherein said gene product is a***

gene product whose activity or amount is reduced by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 521, 1390, 1463, 2782 and 3283. (Emphasis added). Thus, contrary to the Examiner's assertion, this claim language is not commensurate in scope with "any gene product in a cell whose activity or amount is reduced by an antisense, thereby producing a sensitized cell."

In view of the claim language, Applicants maintain that the exemplary antisense nucleic acids, coding sequences and polypeptide gene products that are described in the specification are sufficient to support the elected claim set. As discussed in the previous response, the specification describes several *yph*C genes from a variety of cells, the gene products encoded by those genes, and antisense nucleic acids that are capable of reducing the activity or amount of such *yph*C gene products. The Examiner contends that antisense nucleic acids, which are capable of reducing the activity or amount of a gene product whose activity or amount is reduced by antisense nucleotide sequence selected from the group consisting of SEQ ID NOs: 521, 1390, 1463, 2782 and 3283, are highly variant, and thus, the representative antisense sequences provided by the Applicants are insufficient to show possession of the claimed methods at the time of the invention. The Applicants respectfully disagree with this contention.

In addition to the specific inhibitory antisense nucleic acids complementary to *yph*C that are described in the instant specification and listed in the accompanying sequence listing, the specification describes many other antisense nucleic acids which are capable of reducing the activity or amount of a gene product whose activity or amount is reduced by antisense nucleotide sequence selected from the group consisting of SEQ ID NOs: 521, 1390, 1463, 2782 and 3283. In particular, the specification describes all possible inhibitory antisense nucleic acids complementary to the *yph*C genes recited in the instant application as well as inhibitory antisense sequences upstream and downstream of the *yph*C gene in the operon in which the *yph*C gene is located. This point is appropriately illustrated by Example number 15 of the Written Description Training Materials (available at the USPTO website) which is based on and in accordance with the Written Description Guidelines (66 FR 1099, January 5, 2001) promulgated by the USPTO. Example 15 of the Training Materials sets out a case where the written description of an application supports a claim to broad genus of antisense molecules that inhibit the production of human growth hormone (HGH). In this example, the applicant has disclosed SEQ ID NO: 1 (HGH) and has stated that the invention includes antisense oligonucleotides complementary to

SEQ ID NO: 1. The applicant has also described a method of screening for antisense molecules. The example goes on to state that it well known in the art that a full-length antisense nucleic acid has inhibitory activity as do fragments of the full-length antisense nucleic acid provided that the they match accessible regions of the target nucleic acid. In consideration of the description provided by the applicant in Example 15, the Training Materials go on to state that, in view of the level of knowledge in the art, a skilled artisan would recognize that the applicant possessed the genus embraced by a claim drawn to all antisense nucleic acids complementary to SEQ ID NO: 1 which inhibit HGH production, because the applicant has disclosed a full-length HGH sequence, a functional characteristic of the antisense nucleic acids (the inhibitory function) and a method of screening for such antisense nucleic acids. Accordingly, the Training Materials state that the claim in Example 15 is adequately described.

Like the applicants in Example 15 of the training materials, the instant Applicants have described the full-length *yph*C coding nucleotide sequences for several cells, including both Gram negative and Gram positive bacteria, as well as the full-length complementary sequences (full-length antisense nucleotide sequences). In addition to the full-length antisense, Applicants have provided several working examples describing particular antisense nucleic acids that are complementary to at least a portion of the *yph*C gene and which can be used to sensitize a cell having a *yph*C gene (e.g. sensitizing the cell by inhibiting cellular proliferation). Applicants have also described a method of screening for additional antisense nucleic acids which have activity against the *yph*C gene and products thereof. In particular, Applicants describe a method for introducing an antisense nucleic acid into a cell and determining the extent of the inhibition of cellular proliferation that results (see Example 1 at page 114, line11 to page 120, line 13). Applicants further describe the isolation and characterization of antisense nucleic acids that are determined to have proliferation-inhibiting activity (see Examples 1 and 2 at page 114, line11 to page 123, line 24) and also provide numerous antisense nucleic acids comprising at least, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive nucleotides of a sequences complementary to the *yph*C gene or complementary to a nucleotide sequence encoding a YphC protein which can be screened for activity against the *yph*C gene and it products using the above method (page 97, line 8 to page 102, line 10). Given the description provided in the specification, one of ordinary skill in the art would appreciate that antisense nucleic acid fragments from any portion of the *yph*C gene can be assayed for the ability to inhibit cellular

proliferation. In accordance with Example 15 of the Written Description Training Materials, the instant specification adequately describes all possible inhibitory antisense nucleotide sequences complementary to the *yph*C gene.

In addition to having described antisense nucleotide sequences complementary to *yph*C genes, Applicants have also described antisense nucleotide sequences both upstream and downstream from the *yph*C gene that are in the same operon. In particular, Example 4 of the specification states that due to polar effects, the activity or amount of an essential gene product, which is produced by an essential gene that is located on an operon, may be reduced by an antisense nucleic acid that is not complementary to the essential gene, but rather, is complementary to a gene or nucleotide region upstream of the essential gene in the operon (see page 127, lines 1-10). For many different microbes, the nucleotide sequence both upstream and downstream of the *yph*C gene was well known to those of ordinary skill in the art at the time of filing the instant application. In fact, the instant specification directs those of skill in the art to electronic sequence databases comprising the complete genome sequences for numerous organisms (see page 124, lines 6-21; page 125, lines 36-40; and page 127, lines 17-29). For example, the complete genome of *Haemophilus influenzae* has been known since 1995 (Fleischmann, R.D., et al. 1995. *Science* **269**:496-512 – Exhibit A). The sequencing of the *Escherichia coli* genome was completed in 1997 (Blattner, F.R., et al. 1997. *Science* **277**:1432-4 – Exhibit B), and the genome of *Pseudomonas aeruginosa* was finished in 2000 (Stover, C.K., et al. 2000. *Nature* **406**:959-64 – Exhibit C). In total, the entire genome sequence of at least 40 different microbes was known and publicly available prior to the filing date of the instant application (Exhibit D – see also page 124, lines 6-21). In addition to the foregoing, the instant specification directs those of skill in the art to electronic sequence databases comprising nearly complete or partial genome sequences for additional organisms (see page 124, lines 5-12; page 125, line 40 to page 126, line 3; and page 127, line 30 to page 128, line 4). For example, the genome of *Staphylococcus aureus* was nearly complete at the time of filing the instant application. The complete genome of *S. aureus* was made publicly available on April 21, 2001 (Kuroda, M., et al. 2001. *Lancet* **357**:1218-9 – Exhibit E). Furthermore, at the time of filing, nearly complete genome sequences of many other microbial species were available (see Examples 3 and 4 page123, line 25 to page 129, line 3). Given the public availability of microbial genomes at the time of filing the instant application and the teachings of the

specification, one or ordinary skill in the art would readily appreciate that Applicants demonstrated possession of the full-length coding and antisense sequence of the entire *yph*C operon. Using the same reasoning as described above and presented in Example number 15 of the Written Description Training Materials, a skilled artisan would also appreciate that Applicants have described the all the possible inhibitory antisense sequences that are complementary to at least a portion of the *yph*C operon by describing the full-length antisense sequence complementary to the operon, the function of this sequence and fragments thereof, and a method for determining whether the antisense fragments have the stated inhibitory activity. Accordingly, at the time of filing the instant application, a skilled artisan would have concluded that Applicants possessed the antisense sequences recited in the claimed methods.

In view of the above arguments, Applicants submit that the instant specification provides adequate written description for each of the elected claims (Claims 12, 31, 45-69 and 71-102). Accordingly, Applicants respectfully request that the Examiner withdraw her rejection of Claims 12, 31, 45-69 and 71-102 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 22, 2004

By: [signature]
Jerry L. Hefner
Registration No. 53,009
Attorney of Record
Customer No. 20,995
(619) 235-8550

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1: Science. 1995 Jul 28;269(5223):496-512.

Related Article

Comment in:

- Science. 1995 Jul 28;269(5223):468-70.
- Science. 1995 Sep 29;269(5232):1805.
- Science. 1996 Mar 1;271(5253):1302-3; author reply 1303-4.
- Science. 1996 Mar 1;271(5253):1302; author reply 1303-4.

Whole-genome random sequencing and assembly of Haemophili influenzae Rd.

Fleischmann RD, Adams MD, White O, Clayton RA, Kirkness EF, Kerl AR, Bult CJ, Tomb JF, Dougherty BA, Merrick JM, et al.

Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

An approach for genome analysis based on sequencing and assembly of unse pieces of DNA from the whole chromosome has been applied to obtain the complete nucleotide sequence (1,830,137 base pairs) of the genome from the bacterium Haemophilus influenzae Rd. This approach eliminates the need fo initial mapping efforts and is therefore applicable to the vast array of microbi species for which genome maps are unavailable. The H. influenzae Rd genor sequence (Genome Sequence DataBase accession number L42023) represent only complete genome sequence from a free-living organism.

PMID: 7542800 [PubMed - indexed for MEDLINE]

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Exhibit A

NCBI PubMed National Library of Medicine NLM

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PubMed Central

1: Science. 1997 Sep 5;277(5331):1453-74.

Related Article

Comment in:

- Science. 1997 Sep 5;277(5331):1432-4.
- Science. 1998 Mar 20;279(5368):1827.

Full text article at www.sciencemag.org

The complete genome sequence of Escherichia coli K-12.

Blattner FR, Plunkett G 3rd, Bloch CA, Perna NT, Burland V, Riley M, Collado-Vides J, Glasner JD, Rode CK, Mayhew GF, Gregor J, Davis N Kirkpatrick HA, Goeden MA, Rose DJ, Mau B, Shao Y.

Laboratory of Genetics, University of Wisconsin-Madison, 445 Henry Mall, Madison, WI 53706, USA. ecoli@genetics.wisc.edu

The 4,639,221-base pair sequence of Escherichia coli K-12 is presented. Of 4 protein-coding genes annotated, 38 percent have no attributed function. Comparison with five other sequenced microbes reveals ubiquitous as well a: narrowly distributed gene families; many families of similar genes within E. are also evident. The largest family of paralogous proteins contains 80 ABC transporters. The genome as a whole is strikingly organized with respect to tl local direction of replication; guanines, oligonucleotides possibly related to replication and recombination, and most genes are so oriented. The genome a contains insertion sequence (IS) elements, phage remnants, and many other patches of unusual composition indicating genome plasticity through horizon transfer.

PMID: 9278503 [PubMed - indexed for MEDLINE]

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Exhibit B

NCBI PubMed National Library of Medicine NLM

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ClinicalTrials.gov
PubMed Central

1: Nature. 2000 Aug 31;406(6799):959-64.

Related Article

Comment in:
- Nature. 2000 Aug 31;406(6799):947-8.

nature

Complete genome sequence of Pseudomonas aeruginosa PA01, a opportunistic pathogen.

Stover CK, Pham XQ, Erwin AL, Mizoguchi SD, Warrener P, Hickey M Brinkman FS, Hufnagle WO, Kowalik DJ, Lagrou M, Garber RL, Goltr Tolentino E, Westbrock-Wadman S, Yuan Y, Brody LL, Coulter SN, Fo KR, Kas A, Larbig K, Lim R, Smith K, Spencer D, Wong GK, Wu Z, Pa IT, Reizer J, Saier MH, Hancock RE, Lory S, Olson MV.

PathoGenesis Corporation, Seattle, Washington 98119, USA.

Pseudomonas aeruginosa is a ubiquitous environmental bacterium that is one the top three causes of opportunistic human infections. A major factor in its prominence as a pathogen is its intrinsic resistance to antibiotics and disinfec Here we report the complete sequence of P. aeruginosa strain PAO1. At 6.3 million base pairs, this is the largest bacterial genome sequenced, and the seq provides insights into the basis of the versatility and intrinsic drug resistance aeruginosa. Consistent with its larger genome size and environmental adaptal P. aeruginosa contains the highest proportion of regulatory genes observed fc bacterial genome and a large number of genes involved in the catabolism, tra and efflux of organic compounds as well as four potential chemotaxis system propose that the size and complexity of the P. aeruginosa genome reflect an evolutionary adaptation permitting it to thrive in diverse environments and re the effects of a variety of antimicrobial substances.

PMID: 10984043 [PubMed - indexed for MEDLINE]

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Exhibit C

COMPLETE MICROBIAL GENOMES

BLAST2 on Complete genomes at INFOBIOGEN
(Select BLASTN or TBLASTN and "Genomes Complets")
FASTA on Complete genomes at INFOBIOGEN
(Select FASTA or TFASTA or TFASTX and "Genomes Complets")

Updated, April 6, 2004

		Genome Taxonomy NCBI	Size (Mb)	Base pairs	Date	SRS Accession	Séquences (FASTA) (*)	ID
1		Mycoplasma genitalium	0.58	580,073	Jan 23, 1998	L43967	mgen.seq	mgen.mne
2		Haemophilus influenzae	1.83	1,830,135	Jan 23, 1998	L42023	hin.seq	hin.mne
3		Methanococcus jannaschii	1.66	1,664,970	May 30, 1998	L77117	mjan.seq	mjan.mne
4		Synechocystis sp	3.57	3,573,470	Jan 23, 1998	AB001339	gsyn.seq	gsyn.mne
5		Mycoplasma pneumoniae M129	0.81	816,444	Jan 23, 1998	U00089	mpne.seq	mpne.mne
6		Escherichia coli	4.63	4,638,858	Jan 23, 1998	U00096	ecoli.seq	ecoli.mne
7		Helicobacter pylori strain 26695	1.66	1,667,867	Jun 2, 1998	AE000511	hpyl.seq	hpyl.mne
8		Archaeoglobus fulgidus	2.17	2,178,400	Jan 23, 1998	AE000782	aful.seq	aful.mne
9		Methanobacterium thermoautotrophicum	1.75	1,751,377	Jan 23, 1998	AE000666	mthe.seq	mthe.mne
10		Bacillus subtilis	4.21	4,214,814	Jan 23, 1998	AL009126	bsub.seq	bsub.mne
11		Borrelia burgdorferi	0.91	914,726	Apr 16, 1998	AE000783	bbur.seq	bbur.mne
12		Aquifex aeolicus	1.59	1,595,349	May 30, 1998	AE000657	aaeo.seq	aaeo.mne
13		Pyrococcus horikoshii	1.73	1,738,505	May 30, 1998	AP000001	phor.seq	phor.mne
14		Mycobacterium	4.42	4,420,017	Jun 29,	AL123456	mt.seq	mt.mne

Exhibit D

		tuberculosis H37Rv			1998			
15	■	Treponema pallidum	1.14	1,143,171	Jul 18, 1998	AE000520	tpal.seq	tpal.mne
16	■	Chlamydia trachomatis	1.04	1,047,739	Sep 2, 1998	AE001273	ctra.seq	ctra.mne
17	■	Rickettsia prowazekii	1.11	1,110,773	Nov 15, 1998	AJ235269	rpro.seq	rpro.mne
18	■	Helicobacter pylori strain J99	1.64	1,643,831	Jan 17, 1999	AE001439	hpyl2.seq	hpyl2.mne
19	■	Chlamydia pneumonia	1.23	1,236,350	Mar 16, 1999	AE001363	cpne.seq	cpne.mne
20	■	Pyrococcus abyssi	1.76	1.765,118	July, 1999	AL096836	paby.seq	paby.mne
21	■	Thermotoga maritima	1.8	1,860,725	June 2, 1999	AE000512	tmar.seq	tmar.mne
22	■	Aeropyrum pernix	1.7	1,669,695	June 24, 1999	AP000058	aper.seq	aper.mne
23	■	Deinococcus radiodurans R1	3.0	3,074,955	November 24,1999	AE001825	drad.seq	drad.mne
24	■	Ureaplasma urealyticum	0.8	755,199	February 7, 2000	AE002100	uure.seq	uure.mne
25	■	Campylobacter jejuni NCTC11168	1.7	1,641,481	Feb 14, 2000	CJ11168X1	cjej.seq	cjej.mne
26	■	Chlamydia muridarum	1.08	1,082,508	Mar 10, 2000	AE002269	cmur.seq	cmur.mne
27	■	Chlamydophila pneumoniae AR39	1.24	1,236,093	Mar 10, 2000	AE002164	cppn.seq	cppn.mne
28	■	Neisseria meningitidis MC58	2.3	2,284,651	Mar 13, 2000	AE002098	nmen.seq	nmen.mne
29	■	Neisseria meningitidis Z2491	2.3	2,184,918	Apr 6, 2000	AL162752	nm.seq	nm.mne
30	■	Xylella fastidiosa	2.7	2,729,130	July 15, 2000	AE003850	xfas.seq	xfas.mne
31	■	Vibrio cholerae N16961 El Tor	4.0	4,057,596	Aug 5, 2000	AE003852	vcho.seq	vcho.mne
32	■	Pseudomonas aeruginosa PAO1	6.2	6,,264,403	Sep 7, 2000	AE004091	paer.seq	paer.mne
33	■	Bacillus halodurans C-125	4.2	4,203,003	Sep 17, 2000	BA000004	bhal.seq	bhal.mne
34	■	Halobacterium sp. NRC-1	2.0	2,024,379	Oct 6, 2000	AE004437	hals.seq	hals.mne
		Thermoplasma			Oct 6,			

Exhibit D

35	■	acidophilum	1.56	1,565,106	2000	AL139299	taci.seq	taci.mne
36	▣	Chlamydophila pneumoniae CWL029	1.2	1,200 000	Dec 11, 2000	AE001586	cppp.seq	cppp.mne
37	▣	Chlamydophila pneumoniae J138	1.2	1,200 000	Dec 11, 2000	AP002545	cppo.seq	cppo.mne
38	■	Thermoplasma volcanium GSS1	1.6	1,585,104	Dec 25, 2000	AP000991	tvol.seq	tvol.mne
39	▣	Mesorhizobium loti	7.3	7,036,071	Jan 2, 2001	AP002994	mlot.seq	mlot.mne
40	▣	Escherichia coli O157:H7	5.5	5,500,666	Jan 27, 2001	AE005174	ecoo.seq	ecoo.mne
41	■	Pasteurella multocida PM70	2.2 ?	2,269,587	Feb 7, 2001	AE006034	pmul.seq	pmul.mne
42	▣	Lactococcus lactis subsp. lactis IL1403	2.3	2,378,519	Feb 12, 2001	AE006239	llac.seq	llac.mne
43	▣	Mycobacterium leprae	2.8	3,268,203	Feb 23, 2001	AL450380	mlep.seq	mlep.mne
44	▣	Escherichia coli O157:H7 sub RIMD 0509952	5.5	5,499,400	Mar 22, 2001	BA000007	ecop.seq	ecop.mne
45	▣	Caulobacter crescentus	4	4,038,387	Mar 23, 2001	AE005673	ccre.seq	ccre.mne
46	▣	Streptococcus pyogenes strain SF370 serotype M1	1,8	1,852,442	Apr 17, 2001	AE004092	spyo.seq	spyo.mne
47	▣	Staphylococcus aureus (strain:N315)	2,8	2,838,744	Apr 23, 2001	BA000018	saun.seq	saun.mne
48	▣	Staphylococcus aureus (strain:Mu50)	2,8	2,878,484	Apr 30, 2001	BA000017	sauo.seq	sauo.mne
49	■	Sulfolobus solfataricus	3.0	3,008,365	Apr 30, 2001	AE006641	ssol.seq	ssol.mne
50	■	Mycobacterium tuberculosis CDC1551	4,4	4,420,576	May 2, 2001	AE000516	mtuc.seq	mtuc.mne
51	▣	Mycoplasma pulmonis (strain UAB CTIP)	0.93	963,979	May 17, 2001	AL445566	mpul.seq	mpul.mne
52	▣	Sinorhizobium meliloti plasmid pSymA	1.3	1,361,426	Jul 14, 2001	AE007195	smel.seq	smel.mne
53	▣	Clostridium acetobutylicum ATCC824	4.5	4,155,410	Jul 30, 2001	AE001437	cace.seq	cace.mne
54	▣	Sinorhizobium meliloti chromosome	3.6	3,654,685	Aug 3, 2001	AL591688	smec.seq	smec.mne

Exhibit D

55		Agrobacterium tumefaciens strain C58 circular chromosome	2.8	2,856,721	Aug 21, 2001	AE007869	atum.seq	atum.mne
56		Streptococcus pneumoniae TIGR4	2.2	2,172,327	Sep 2, 2001	AE005672	spne.seq	spne.mne
57		Streptococcus pneumoniae R6	2.0	2,049,595	Sep 9, 2001	AE007317	spnf.seq	spnf.mne
58		Sulfolobus tokodaii	2.6	2,695,206	Sep 19, 2001	BA000023	stok.seq	stok.mne
59		Rickettsia conorii Malish 7	1.3	1,275,535	Sep 19, 2001	AE006914	rcon.seq	rcon.mne
60		Agrobacterium tumefaciens strain C58 linear chromosome	2.0	2,085,892	Sep 21, 2001	AE007870	atul.seq	atul.mne
61		Yersinia pestis strain CO92	4.6	4,654,678	Oct 6, 2001	AL590842	ypes.seq	ypes.mne
62		Listeria innocua Clip11262	3.0	3,011,758	Oct 27, 2001	AL592022	linn.seq	linn.mne
63		Listeria monocytogenes strain EGD	2.9	2,945,078	Oct 27, 2001	AL591824	lmon.seq	lmon.mne
64		Salmonella typhimurium LT2	4.8	4,870,812	Oct 28, 2001	AE006468	sthy.seq	sthy.mne
65		Salmonella enterica serovar Typhi	4.8	4,809,987	Oct 28, 2001	AL513382	sthi.seq	sthi.mne
66		Nostoc sp PCC 7120	6.4	6,414,671	Nov 30, 2001	BA000020	nost.seq	nost.mne
67		Brucella melitensis strain 16M chromosomes I and II	3.3	3,312,931	Dec 29, 2001	AE008917 AE008918	bmel.seq	bmel.mne
68		Clostridium perfringens	3.0	3,031,880	Jan 16, 2002	BA000016	cper.seq	cper.mne
69		Pyrobaculum aerophilum strain IM2	2.2	2,234,390	Jan 18, 2002	AE009441	pyra.seq	pyra.mne
70		Ralstonia solanacearum GMI1000	5.8	5,812,322	Feb 01, 2002	AL646052 AL646053	rsol.seq	rsol.mne
71		Pyrococcus furiosus DSM 3638	1.9	1,918,246	Feb 27, 2002	AE009950	pfur.seq	pfur.mne
72		Wigglesworthia brevipalpis	0.7	697,721	Mar 4, 2002	BA000021	wbre.seq	wbre.mne
73		Fusobacterium nucleatum subsp. nucleatum ATCC 25586	2.1	2,186,280	Mar 27, 2002	AE009951	fnum.seq	fnum.mne

74	■	Streptococcus pyogenes strain MGAS8232	1,9	1,905,297	Mar 29, 2002	AE009949	spyg.seq	spyg.mne
75	■	Methanopyrus kandleri AV19	1.7	1,703,889	Apr 4, 2002	AE009439	mkan.seq	mkan.mne
76	■	Methanosarcina acetivorans str. C2A	5.7	5,783,472	Apr 5, 2002	AE010299	mace.seq	mace.mne
77	■	Thermoanaerobacter tengcongensis strain MB4T	2.7	2,703,405	May 9, 2002	AE008691	tten.seq	tten.mne
78	■	Streptomyces coelicolor	8.0	8,707,150	May 9, 2002	AL645882	scoe.seq	scoe.mne
79	■	Methanosarcina mazei strain Goe1	4.1	4,119,025	May 21, 2002	AE008384	mmaz.seq	mmaz.mne
80	■	Xanthomonas campestris pv. str. ATCC 33913	5.1	5,103,728	May 29, 2002	AE008922	xcam.seq	xcam.mne
81	■	Xanthomonas axonopodis pv. citri str. 306	5.2	5,203,494	May 29, 2002	AE008923	xaxo.seq	xaxo.mne
82	▣	Staphylococcus aureus (strain:MW2)	2,8	2,841,566	May 30, 2002	BA000033	sauw.seq	sauw.mne
83	■	Corynebacterium glutamicum ATCC 13032	3.3	3,309,851	June 6, 2002	BA000036	cglu.seq	cglu.mne
84	■	Buchnera aphidicola str.	0.6	644,814	July 3, 2002	AE013218	baph.seq	baph.mne
85	■	Chlorobium tepidum TLS	2.1	2,166,446	July 4, 2002	AE006470	ctet.seq	ctet.mne
86	▣	Streptococcus pyogenes strain MGAS315	1,9	1,902,681	Jul 20, 2002	AE014074	spyq.seq	spyq.mne
87	▣	Yersinia pestis strain KIM	4.6	4,625,545	Jul 29, 2002	AE009952	ypet.seq	ypet.mne
88	▣	Thermosynechococcus elongatus BP-1	2.5	2,594,257	Aug 31, 2002	BA000039	telo.seq	telo.mne
89	▣	Oceanobacillus iheyensis	3,5	3,631,128	Sep 14, 2002	BA000028	oihe.seq	oihe.mne
90	▣	Streptococcus agalactiae NEM316	1,3	1,313,350	Sep 19, 2002	AL732656	saga.seq	saga.mne
91	▣	Streptococcus agalactiae serotype V	2,1	2,166,207	Sep 19, 2002	AE009948	sagv.seq	sagv.mne
92	▣	Bifidobacterium longum NCC2705	2.2	2,268,766	Sep 27, 2002	AE014295	blon.seq	blon.mne

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93		Brucella suis 1330 chr II	1.2	1,213,801	Oct 4, 2002	AE014292	bsui.seq	bsui.mne
94		Corynebacterium efficiens YS-314	3.1	3,147,590	Oct 5, 2002	BA000035	ceff.seq	ceff.mne
95		Shigella flexneri 2a str. 301	4.6	4,631,693	Oct 18, 2002	AE005674	sfle.seq	sfle.mne
96		Streptococcus mutans UA159	2.0	2,031,491	Oct 28, 2002	AE014133	smut.seq	smut.mne
97		Shewanella oneidensis MR-1	5.0	4,996,813	Dec 05, 2002	AE014299	sone.seq	sone.mne
98		Pseudomonas putida KT2440	6.1	6,183,063	Dec 16, 2002	AE015451	pput.seq	pput.mne
99		Mycoplasma penetrans	1.4	1,358,833	Dec 16, 2002	BA000026	mpen.seq	mpen.mne
100		Vibrio vulnificus CMCP6	5.2	5,127,698	Dec 26, 2002	AE016795 AE016796	vvul.seq	vvul.mne
101		Bradyrhizobium japonicum	9.1	9,107,328	Dec 26, 2002	BA000040	bjap.seq	bjap.mne
102		Escherichia coli CFT073	5.2	5,232,448	Dec 26, 2002	AE014075	ecoq.seq	ecoq.mne
103		Staphylococcus epidermidis ATCC 12228	2.5	2,499,759	Jan 3, 2003	AE015929	sepi.seq	sepi.mne
104		Clostridium tetani E88	2.8	2,799,791	Feb 8, 2003	AE015927	cttn.seq	cttn.mne
105		Lactobacillus plantarum strain WCFS1	3.3	3,308,774	Feb 9, 2003	AL935263	lpla.seq	lpla.mne
106		Xylella fastidiosa Temecula1	2.5	2,520,282	Feb 9, 2003	AE015929	xfat.seq	xfat.mne
107		Tropheryma whipplei TW08/27	0.9	926,038	Feb 19, 2003	BX072543	twhi.seq	twhi.mne
108		Vibrio parahaemolyticus	5.1	5,166,520	Mar 7,2003	BA000031 BA000032	vpar.seq	vpar.mne
109		Coxiella burnetii strain RSA 493	1.9	1,995,635	Apr 6,2003	AE016828	cbur.seq	cbur.mne
110		Streptomyces avermitilis	9.0	9,027,058	Apr 9,2003	BA000030	save.seq	save.mne
111		Chlamydophila caviae GPIC	1.1	1,173,570	Apr 16, 2003	AE015925	ccav.seq	ccav.mne
112		Bacillus subtilis	5.4	5,412,829	Apr 17, 2003	AE016877	bcer.seq	bcer.mne

Exhibit D

113	■	Leptospira interrogans serovar lai str. 56601	4.3	4,355,921	Apr 30, 2003	AE010300	lint.seq	lint.mne
114	■	Nitrosomonas europaea ATCC 19718	2.8	2,812,544	May 5, 2003	AL954747	neur.seq	neur.mne
115	■	Bacillus anthracis str. Ames	5.2	5,228,313	May 5, 2003	AE016879	bant.seq	bant.mne
116	■	Mycoplasma gallisepticum strain R	0.9	996,602	June, 11, 2003	AE015450	mgal.seq	mgal.mne
117	■	Mycobacterium bovis AF2122/97	4.3	4,346,142	June, 13, 2003	BX248333	mbov.seq	mbov.mne
118	■	Helicobacter hepaticus ATCC 51449	1.8	1,799,446	Jun 28, 2003	AE017125	hhep.seq	hhep.mne
119	■	Pirellula sp. strain 1	7.1	7,146,726	Jun 30, 2003	BX119912	pisp.seq	pisp.mne
120	■	Haemophilus ducreyi 35000HP	1.6	1,699,255	Aug 4, 2003	AE017143	hduc.seq	hduc.mne
121	■	Chlamydophila pneumoniae TW-183	i1.2	1,226,115	Aug 4, 2003	AE009440	cpnt.seq	cpnt.mne
122	■	Prochlorococcus marinus subsp. marinus str. CCMP1375	1.7	1,751,380	Aug 4, 2003	AE017126	pmas.seq	pmas.mne
123	■	Prochlorococcus marinus MED4	1.6	1,658,190	Aug 19, 2003	BX548174	pmar.seq	pmar.mne
124	■	Prochlorococcus marinus MIT9313	2.4	2,411,173	Aug 19, 2003	BX548175	pmat.seq	pmat.mne
125	■	Tropheryma whipplei str. Twist	0.9	927,423	Aug 19, 2003	AE014184	twht.seq	twht.mne
126	■	Synechococcus sp. WH8102	2.4	2,434,728	Aug 19, 2003	BX548020	syns.seq	syns.mne
128	■	Bordetella pertussis strain Tohama I	4.1	4,086,739	Aug 19, 2003	BX640420	bper.seq	bper.mne
129	■	Bordetella bronchiseptica strain RB50	5.3	5,339,929	Aug 19, 2003	BX470250	bbro.seq	bbro.mne
130	■	Bordetella parapertussis strain 12822	4.8	4,774,201	Aug 19, 2003	BX470249	bpar.seq	bpar.mne
131	■	Chromobacterium violaceum ATCC 12472	4.7	4,751,980	Aug 31, 2003	AE016825	cvio.seq	cvio.mne
132	■	Porphyromonas gingivalis W83	2.3	2,343,896	Sep 4, 2003	AE015924	pgiv.seq	pgiv.mne
133	■	Pseudomonas syringae pv. tomato str. DC3000	6.4	6,398,326	Sep 5, 2003	AE016853	psyn.seq	psyn.mne

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134		Wolinella succinogenes	2.1	2,110,655	Sep 8, 2003	BX571656	wsuc.seq	wsuc.mne
135		Gloeobacter violaceus PCC 7421	4.6	4,659,769	Sep 28, 2003	BA000045	gvio.seq	gvio.mne
136		Photorhabdus luminescens subsp. laumondii TTO1	5.6	5,689,787	Sep 30, 2003	BX470251	plum.seq	plum.mne
137		Geobacter sulfurreducens PCA	4.4	4,426,126	Dec 30, 2003	AE017180	gsul.seq	gsul.mne
138		Nanoarchaeum equitans Kin4-M	0.5	490,885	Dec 30, 2003	AE017199	nequ.seq	nequ.mne
139		Bdellovibrio bacteriovorus	3.7	3,783,450	Feb 5, 2004	BX842601	bbac.seq	bbac.mne
140		Lactobacillus johnsonii NCC 533	1.9	1,993,036	Feb 5, 2004	AE017198	ljoh.seq	ljoh.mne
141		Mycobacterium avium subsp. paratuberculosis str. k10	4.8	4,830,681	Feb 5, 2004	AE016958	mavi.seq	mavi.mne
142		Treponema denticola ATCC 35405	2.8	2,843,741	Feb, 9, 2004	AE017226	tden.seq	tden.mne
143		Wolbachia endosymbiont	1.2	1,268,022	Feb, 13, 2004	AE01722 6	wend.seq	wend.mne
144		Mycoplasma mycoides subsp. mycoides SC	0.3	347,558	Feb, 13, 2004	BX293980	mmyc.seq	mmyc.mne
145		Thermus thermophilus HB27	1.8	1,895,237	Apr 6, 2004	AE017221	tthe.seq	tthe.mne

(*) The FASTA sequences are the collection of entries in GenBank for the genome of the corresponding species. It may be some overlap in the differents entries. For an access to the entire sequence (in one entry) see : ftp://ftp.ebi.ac.uk/pub/databases/genomes/Bacteria/ or ftp://ftp.ncbi.nih.gov/genomes/Bacteria/

Data on Microbial Genomes at INFOBIOGEN

- Incomplete genomes
- Genomes in FASTA format
- Other links for microorganism genomes
- DEAMBULUM (Prokaryota genomes)
- BLAST2 on incomplete genomes is also possible (as a tool) using SRS6
- **EMGLib SRS** Coding sequences of completed genomes
- **EMGPep SRS** Protein sequences of completed genomes

Others links

Exhibit D

- **EMGLib** Enhanced Microbial Genomes Library - PBIL Lyon
- **MICADO** INRA - Jouy en Josas
- **COLIPAGE** Institut de Génétique - Orsay
- Completed Genomes at the EBI
- **Directory /genomes/Bacteria - EBI FTP**
- Genome Centers and Databases - NCBI
- Complete Genomes - NCBI
- **Microbial genomes - NCBI all formats**
- **Directory /genomes/Bacteria on NCBI FTP**

- GOLD : Genomes OnLine Database (Nikos Kirpides)
- Complete genome papers
- Genome sequencing projects (Terry Gaasterland)
- TIGR Microbial Database
- MUMmer: The Whole Genome Alignment Tool - TIGR
- The Comprehensive Microbial Resource Home Page - TIGR
- Sequenced Genomes - Genome News Network
- Complete genomes in KEGG
- Completely Sequenced Genomes - Rockefeller
- SACSO: Systematic Analysis of Completely Sequenced Organisms
- DNA Structural Analysis of Complete Genomes and Chromosomes CBS - Denmark
- MBGD Microbial Genome Database for Comparative Analysis - Japan
- PEDANT - Genome analysis and annotation at MIPS
- HAMAP High quality Automated Microbial Annotation of Proteomes HAMAP Links
- WIT2 View Models : 53 genomes

- Complete proteomes - Expasy
- Bacterial Up-to-date nomenclature

- Taxonomy - NCBI
- Life on Earth

Comments and suggestions to: [dessen@infobiogen.fr]

Exhibit D

1: Lancet. 2001 Apr 21;357(9264):1225-40.

Comment in:

- Lancet. 2001 Apr 21;357(9264):1218-9.

Whole genome sequencing of meticillin-resistant Staphylococcus aureus.

Kuroda M, Ohta T, Uchiyama I, Baba T, Yuzawa H, Kobayashi I, Cui L Oguchi A, Aoki K, Nagai Y, Lian J, Ito T, Kanamori M, Matsumaru H, Maruyama A, Murakami H, Hosoyama A, Mizutani-Ui Y, Takahashi NI Sawano T, Inoue R, Kaito C, Sekimizu K, Hirakawa H, Kuhara S, Goto Yabuzaki J, Kanehisa M, Yamashita A, Oshima K, Furuya K, Yoshino C Shiba T, Hattori M, Ogasawara N, Hayashi H, Hiramatsu K.

Hiramatsu, Department of Bacteriology, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, 113-8421, Tokyo, Japan.

BACKGROUND: Staphylococcus aureus is one of the major causes of community-acquired and hospital-acquired infections. It produces numerous including superantigens that cause unique disease entities such as toxic-shocl syndrome and staphylococcal scarlet fever, and has acquired resistance to practically all antibiotics. Whole genome analysis is a necessary step toward: future development of countermeasures against this organism. METHODS: \ genome sequences of two related S aureus strains (N315 and Mu50) were determined by shot-gun random sequencing. N315 is a meticillin-resistant S aureus (MRSA) strain isolated in 1982, and Mu50 is an MRSA strain with vancomycin resistance isolated in 1997. The open reading frames were identi by use of GAMBLER and GLIMMER programs, and annotation of each was with a BLAST homology search, motif analysis, and protein localisation prediction. FINDINGS: The Staphylococcus genome was composed of a con mixture of genes, many of which seem to have been acquired by lateral gene transfer. Most of the antibiotic resistance genes were carried either by plasmi by mobile genetic elements including a unique resistance island. Three classe new pathogenicity islands were identified in the genome: a toxic-shock-synd toxin island family, exotoxin islands, and enterotoxin islands. In the latter tw pathogenicity islands, clusters of exotoxin and enterotoxin genes were found closely linked with other gene clusters encoding putative pathogenic factors. analysis also identified 70 candidates for new virulence factors. INTERPRETATION: The remarkable ability of S aureus to acquire useful ge

Exhibit E

from various organisms was revealed through the observation of genome complexity and evidence of lateral gene transfer. Repeated duplication of gei encoding superantigens explains why S aureus is capable of infecting human diverse genetic backgrounds, eliciting severe immune reactions. Investigatioı many newly identified gene products, including the 70 putative virulence fac will greatly improve our understanding of the biology of staphylococci and tl processes of infectious diseases caused by S aureus.

PMID: 11418146 [PubMed - indexed for MEDLINE]

Exhibit E